REMARKS/ARGUMENTS

The above amendments have been provided based on the format described at 1265 Off. Gaz. Pat. Office 87 (December 17, 2002) and as authorized by Deputy Commissioner for Patents, Stephen Kunin on January 31, 2003.

Claims 2-4, 12, 13, 15-21, and 27 were pending. The Examiner withdrew 1-10 and 16-20 from consideration following a restriction requirement. Claims 2-4, 12, 13, 15-21, and 27 were rejected in the previous Office action, and no claims were allowed. Claims 15, 17 and 27 are amended herein. Please cancel claims 1-10 and 16-20 without prejudice. Claims 2-4, 12, 13, 15-21, and 27 are currently pending. A clean copy of the amended claims are provided as Exhibit A for the convenience of the Office.

Formal Matters

Applicants gratefully acknowledge the entry of the Amendments filed 6/10/02 (Paper No. 54), 8/23/01 (Paper No. 45), 2/5/01 (Paper No. 39), and 12/18/01.

A review of the record shows some ambiguity in the designation of application for which benefit of priority is claimed. Applicants hereby state that the priority date for the claimed subject matter is claimed only to April 5, 1994, the filing date of 08/222,851, now U.S. Patent 5,273,128, for which the instant application is a continuation in part. Benefit of any earlier application is hereby disclaimed.

The Office objects to the peptide sequences corresponding to SEQ ID NO: 40-42 because the added material is allegedly new matter. Applicants respectfully traverse this rejection in light of the specification as originally filed. Supporting disclosure for SEQ ID NOs: 40-42 is found throughout the application. For example, at page 11, lines 4-9, Applicants disclose the peptide sequences RIALRY and RILLRY and these sequences read in reverse as preferred embodiments of the α and β peptides. SEQ ID NO: 40 is an inverted repeat of the RIALRY sequence and SEQ ID NOs: 41 and 42 are heterodimers of RIALRY and RILLLRY. Therefore, the addition of the sequences does not represent new matter.

In light of the above, Applicants respectfully submit that the objection to the specification has been overcome. Therefore, Applicants request the withdrawal of the objection.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 2-4, 12, 13, 15-21, and 27 are rejected under 35 U.S.C. § 112, first paragraph as allegedly including material that is not supported by the disclosure as filed. Specifically, the Office asserts that the peptide sequences corresponding to SEQ ID NOs: 40-42 in claim 15 and the phrase "consists of 12 to 60 amino acids" in claim 27 have no basis in the original disclosure. Applicants respectfully traverse this rejection for the reasons discussed below.

As discussed above, the peptide sequences corresponding to SEQ ID NOs: 40-42 are specifically disclosed in the instant specification, and thus the written description requirement of 35 U.S.C. § 112, first paragraph is satisfied.

The phrase "consists of 12 to 60 amino acids" in claim 27 finds support in the instant specification at page 4, lines 16-28. The claimed compounds are disclosed as dimers "containing a minimum of 12 amino acids". *See* specification, at page 4, line 19-20. The upper range of the claimed compounds is also disclosed as "up to 60 amino acids." *See* specification, at page 4, line 27. Therefore, the specification clearly discloses to the skilled artisan that the inventors considered compounds of a minimum of 12 amino acids to a maximum of 60 amino acids to part of the invention, and thus the phrase "consists of 12 to 60 amino acids" is inherently supported by the disclosure in the original specification. Nonetheless, to expedite prosecution, the claim has been amended herein to recite "up to 60 amino acids."

In light of the above remarks, Applicant respectfully submits that the rejection under 35 U.S.C. § 112, first paragraph is overcome. Therefore, Applicants request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 2-4, 12, 13, 15-21, and 27 are rejected under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. According to the Action, claim 15 is indefinite in the recitation of "wherein comprises." The Action asserts that claim 27 is indefinite in the recitation of "consists of 12 to 60

amino acids, and has the one of the following structures." The Action states that the SEQ ID NOs recited in claim 27 each have 10 amino acids in length. The Action further asserts that claim 15 is indefinite in the recitation of peptides with the sequences of SEQ ID NOs: 36 and 40-42 because the peptides lack antecedent basis in claim 27. According to the Action, claim 17 is indefinite in the recitation of SEQ ID NO: 36 because the peptide lacks antecedent basis in claim 27. Applicants traverse these rejections.

Claim 15 is amended to clarify the recitation "wherein comprises". As the amended claim 15 is an independent claim, the antecedent basis rejection is now moot.

Claim 27 is amended herein to clarify the phrase "and has one of the following structures" to indicate that the claimed peptide dimer comprises one of the amino acid sequences disclosed in the claim. Claim 27 as amended claims a peptide dimer "up to 60 amino acids", therefore the disclosed 10 amino acid sequence within this dimer does not render the claim indefinite.

Amended claim 17 depends from claim 15, therefore the antecedent basis rejection is now moot.

In light of the above remarks, Applicant respectfully submits that the rejection under 35 U.S.C. § 112, second paragraph is overcome. Therefore, Applicants request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103(a)

Claims 2-4, 12, 13, 18-21, and 27 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Olsson (U.S. Patent No. 5,073,540) or Krensky (WO 88/05784) for reasons of record. To summarize, the Action asserts that Olsson discloses compounds with "essentially the same structure" as the instant application. The Action further asserts that Krensky also discloses similar peptides and the use of conventional techniques to extend the half-lives of those peptides. Moreover, the Examiner takes the position that a skilled artisan would expect dimers of the same unit to exert the same functional effects as a monomer. Applicants traverse this rejection.

1. The cited references do not render the claimed compositions prima facie obvious.

Applicants respectfully submit that a *prima facie* case for obviousness has not been presented. The claimed compositions relate to homodimeric and heterodimeric peptides comprising HLA-B α1 domain sequences that inhibit cytotoxicity. Therefore, a *prima facie* case of obviousness requires that (1) the reference teach or suggest dimeric peptides of HLA-B α1 domain sequences that are inhibitory to cytotoxicity or (2) the references must provide a motivation to modify the teachings of the reference to result in the claimed compositions, as well as a reasonable expectation of success in modifying the teachings. MPEP § 2142 (8th ed. 2001).

In the obviousness analysis required under 35 U.S.C. § 103(a), the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Any disclosure teaching away from the claimed invention also must be considered in the obviousness analysis. MPEP § 2142.01. The fact that an invention can be modified is insufficient to establish prima facie obviousness in the absence of a suggestion or motivation to make such a modification. *Id.* Furthermore, if a modification changes the principle of operation of a reference, the teachings of that reference do not render the claimed invention obvious. *Id.* Finally, in the analysis of prior art references, it is improper to exercise hindsight to select bits and pieces from the references to create a motivation to modify that is not found in the references, but only in the applicant's disclosure. *In re Dow Chemical Co.* 5 U.S.P.Q.2d § 1529, 1531 (Fed. Cir. 1988). Simply stated, the suggestion or motivation to modify a reference must be found in the prior art.

Olsson does not teach or suggest peptide dimers comprising amino acids sequences related to Class I HLA-B α1 domain to modulate cytotoxicity. Olsson discloses the use of compositions that comprise two sequences that bind two different cell surface receptors. The two cell surface receptors are Class I MHC molecules and a second cell surface receptor molecule. *See* column 2, lines 29-35. Olsson's second cell surface receptor is disclosed as including endocrine, paracrine,

and autocrine receptors, adrenergic receptors, lipoprotein receptors, opiate receptors, and steroid receptors. *See* column 2, line 49 to column 3, line 4. Thus, while Olsson describes peptide comprising Class I MHC sequences, these MHC peptides are never discussed as independent of the sequences that also bind the second receptor. Simply stated, Olsson fails to teach the use of Class I MHC peptides alone. *See, e.g.*, Claim 1. Olsson's invention lies in Class I MHC peptides that also bind a second cell surface receptor, a fundamentally different peptide than that of the instant application. Because Olsson does not describe or discuss the use of peptides comprising HLA-B α1 sequences or peptide dimers comprising such sequences, the definitive element of the claimed invention - dimeric peptides comprised of HLA-B sequences - is completely absent.

Krensky also does not teach or suggest peptide dimers comprising HLA-B sequences. Rather, Krensky discloses the use of class I MHC monomers to inhibit cytotoxicity. Numerous modifications including adding detectable label, enzymes, and antibodies are disclosed. However, dimerization of the disclosed sequences to result in homodimers or heterodimers is never discussed or described by Krensky.

Furthermore, a person of ordinary skill in the art would not have modified the teachings of Olsson to create peptide dimers of Class I MHC sequences. First, Olsson never suggests or teaches any modification of the disclosed peptides to include only sequences that interact with a single cell surface receptor. Second, Olsson expressly teaches the use of a peptide that binds two different cell surface molecules to elicit the desired effect. Therefore, Olsson actually teaches away from modifying his invention to create peptide dimers of Class I MHC sequences, since Olsson requires two different peptide sequences binding two different cell surface receptors. Third, the principle of operation for the Olsson invention would be altered by using dimeric peptides that interact with only one cell surface receptor. In the absence of any teaching or suggestion regarding the modification of its peptides to create the Applicants' dimeric peptide of Class I MHC sequences , it is impossible to convey any reasonable expectation of success. Thus, Olsson does not establish *prima facie* obviousness.

Likewise, the skilled artisan would not be motivated to modify the teachings of Krensky to create peptide dimers of Class I MHC sequences. Krensky never suggests or teaches any modification of the disclosed peptides to include dimeric sequences. In the complete absence of such teaching or suggestion to modify the disclosed peptide, Krensky cannot provide a reasonable

expectation for success for such modification, and thus does not render the claimed invention obvious.

In sum, Olsson and Krensky fail to teach or suggest the claimed compositions or suggest any modification of their teachings that result in the claimed compositions. Thus, Olsson and Krensky do not render the claimed compositions *prima facie* obvious.

2. The unexpected superior activity of the peptide dimers renders the peptide nonobvious to the skilled artisan.

Applicants respectfully submit that what is unexpected to the skilled artisan is not obvious. *In re Soni*, 34 U.S.P.Q.2d 1684 (Fed. Cir. 1995). Applicants respectfully submit that evidence disclosed by Applicants in the specification discloses the unexpected efficacy of peptide dimers, rendering these peptides functionally distinct from the peptide monomers. On page 22 of the specification, lines 1-9, Applicants disclose the results of actual experiments performed with peptide monomers and dimers of Class I MHC sequences. While the monomers reduced cytotoxicity, the inverted dimer B2702.84-75/75-84 and the homodimer B2702.75-84/75-84 are unexpectedly superior to the monomer in their ability to completely inhibit cytotoxicity. *See* specification, at page 22, lines 5-9. Hence, this evidence proves that monomers do not exert the same effect as dimers of the same unit. Moreover, the peptide dimers are unexpectedly more effective in their complete inhibition of cytotoxicity. If the Office does not accept the accuracy of these results, Applicants respectfully request the Office articulate a factual basis or scientific reasoning for why it doubts the truth or accuracy of these results.

The Office asserts that the skilled artisan would expect dimers of the same unit to exert the same functional effects as a monomer. Applicants respectfully submit that there must be some clear evidence to establish why the modification would have been obvious which can properly qualify as prior art. *In re Kaplan*, 229 U.S.P.Q.2d 678, 683 (Fed. Cir. 1986). The Office is required to provide more than a mere assertion that the acknowledged differences between the cited references and the claimed subject matter would have been obvious to the skilled artisan. If the rejection is only based upon facts within the personal knowledge of the Examiner and such facts must be supported by an affidavit from the Examiner in accordance with 37 C.F.R. 1.104(d)(2). This appears to be the case

here. Accordingly, Applicants respectfully request an affidavit from the Examiner if the Office maintains the argument that dimers of the same unit have the same effect as that of the monomer.

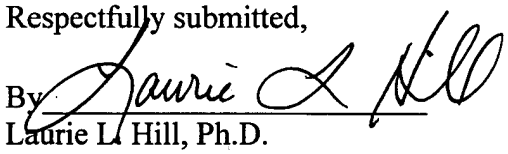
In light of the above remarks, Applicant respectfully submits that the rejection under 35 U.S.C. § 103(a) is overcome. Therefore, Applicants request the withdrawal of this rejection.

CONCLUSION

Applicants submit that the objections and the rejections under 35 U.S.C. §§ 112 and 103(a) have been overcome by the above amendments and remarks. Early allowance of pending claims 2-4, 12, 13, 15-21, and 27 is respectfully requested. In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 286002020023.

Dated: May 30, 2003

Respectfully submitted,

By 

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